



DATSD(CBD)

Biological Weapons and Bioterrorism Threats: *The role of vaccines in protecting the military and civilian sectors*

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Outline

- **Threats**
- **DoD Medical Biological Defense Capabilities**
- **Responses**
 - Military
 - Civilian

Potential BW Threats

Bacteria

Anthrax

Plague

Tularemia

Brucellosis

Q-Fever

Glanders

Cholera

Typhus

Shigellosis

Virus

Smallpox

Encephalomyelitis

Ebola

Marburg

Toxin

Botulinum

(Types A-F)

Staphylococcal
Enterotoxins (SEB)

Ricin

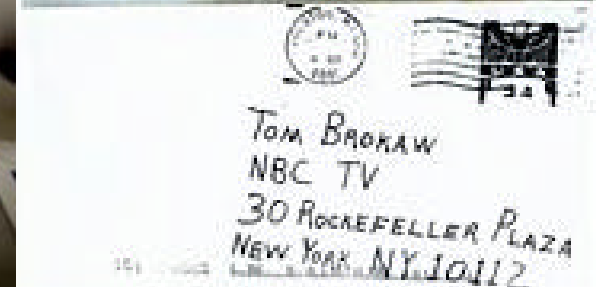
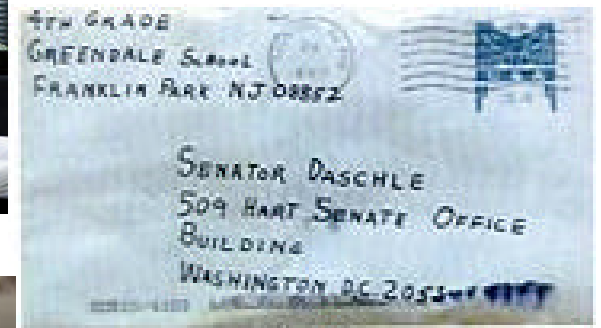
Marine
Neurotoxins

Mycotoxins

Clostridium
Perfringens

Bioterrorism Threats

...to reality.



Why Vaccinate?

- **Biological warfare (BW) agents pose high risk to military forces and operations**
 - At least 10 countries pursuing BW programs
- **Vaccines are lowest risk, most effective protection**
 - More effective with fewer adverse effects than antibiotics or other treatments
 - Enable force projection by providing continuous, long-lasting protection
- **No real-time detection systems currently available**
 - Identification delayed 15-45 minutes after exposure
- **Masks must be worn to be effective**

Requirement

- **DoD policy stated in DoD Directive 6205.3 to “...develop a capability to acquire and stockpile adequate quantities of vaccines to protect the programmed force against all validated biological warfare threats.”**

Chronology of Considerations for BD Vaccine Production

1991/92

June 93

Aug 94

Jan 95

1996

↑ (Joint Program Office for Biological Defense Established)

GOCO



- *Why Started?* Lessons From ODSS
 - No Surge Capacity for BD Vaccines
 - Limited Industry Interest
- *Why Stopped?* DOD and Congressional Directives
 - Need for Dedicated DOD Facility?
 - Most Economical Approach?

COCO



- *Why Modified?* Affordability
 - ADM Directed Cost/Benefit Analysis
 - \$450M Unfunded Requirement FY96-01
 - Industry Survey

Prime Systems Contract Approach

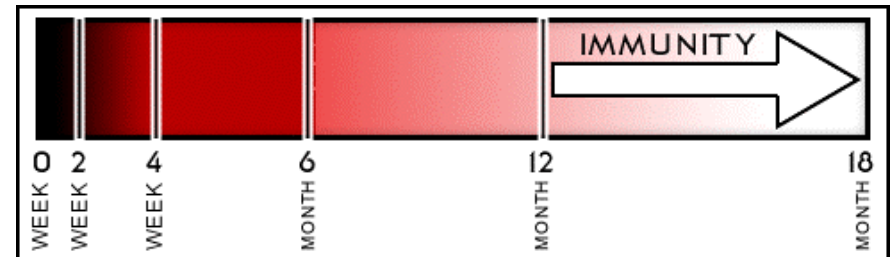
- *Why Started?* **Optimum Resource Utilization**
 - Reduces Requirement for New Facilitization
 - Enhances Competition
- Directed Prime Systems Contract Approach
- Prime System Contract Awarded (Nov-1997)

What Does Producing a Vaccine Mean?

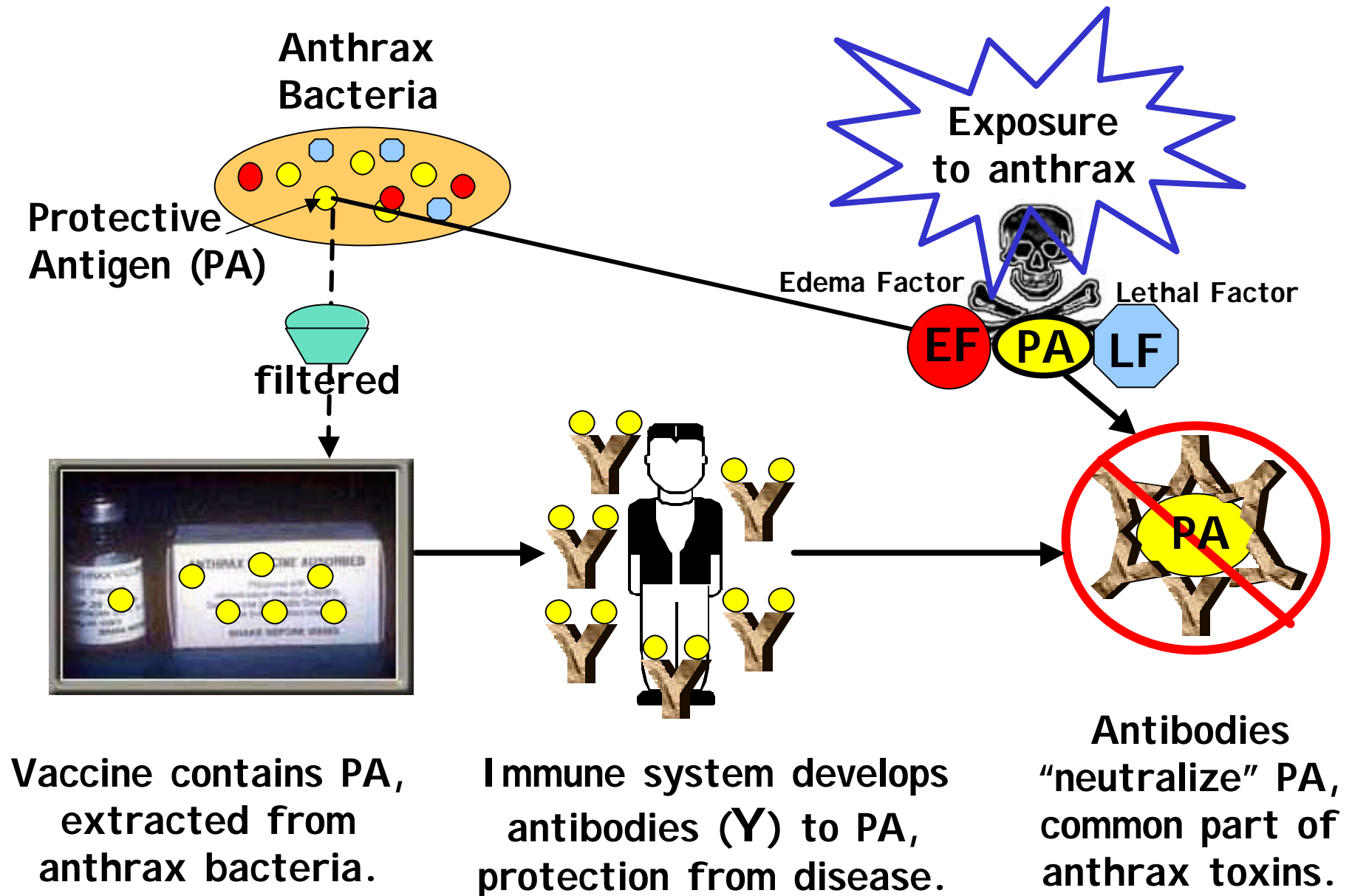
| | SCIENCE & TECHNOLOGY | DEVELOPMENT & LICENSURE | LICENSED PRODUCTION |
|----------------------------|--|---|--|
| Production Approach | Bench top – many approaches | Scale up – best approach | Full Scale – fixed method |
| Vaccine Recipients | Lab animals (10^2-10^3) | Volunteers (10^3) | Population (10^6) |
| Data Management | Lab notebook | Master File: mfrng and release data, clinical trials, validation studies | Mfrng and release data, post market surveillance, adverse reactions |
| Stakeholders | Scientist, science manager, User | Scientist, product mgr., FDA, manufacturer, User | Warfighter, medic, logistician, FDA, mfr., product mgr. |
| Production Risk | Moderate | High | Low |
| Overall Risk | Low | High | Low–High |

Anthrax Vaccine Adsorbed

- **Approved by the FDA in 1970 (Only licensed BD vaccine)**
- **Cell-free filtrate, produced by a strain of anthrax that does not cause disease.**
- **Safely and routinely administered to at-risk wool mill workers, veterinarians, laboratory workers, and livestock handlers in the United States**
- **Manufactured by BioPort Corporation**
- **Currently requires 6 shots & annual booster to maintain full immunity**
 - Study underway by CDC to investigate fewer doses in series (reduce to 3-4 shots)



How Anthrax Vaccine Prevents Disease



Anthrax Vaccine Efficacy against Inhalation Challenge

- Efficacy of current vaccine based on bacterial construct (that is, Protective Antigen binding to Lethal Factor and Edema Factor) not on route of exposure.
- Brachman study suggests efficacy in humans against inhalational anthrax
 - 5 cases of inhalational anthrax (4 fatal) among non-vaccinated individuals (n = 754)
 - Zero cases of inhalation anthrax among vaccinated individuals (n = 379)

Vaccine Efficacy Against Aerosol Challenge

| | Vaccinated | | Control | |
|-----------------|------------|------------|---------|------------|
| | Number | Percentage | Number | Percentage |
| Rabbits | 62 of 65 | 95 | 0 of 18 | 0 |
| Rhesus Macaques | 114 of 117 | 97 | 0 of 28 | 0 |

Concerns for Developing & Producing Biological Defense Vaccines

- **Limited interest from industry**
 - Most Public Health needs are fulfilled by the private sector
 - BD Vaccines similar to orphan drugs (interest from a few small to mid-size companies)
- **Identifying surrogate markers of efficacy**
 - Animal models used to validate efficacy of vaccines
 - Limited human efficacy data available
 - FDA review of 21 CFR requirement for Phase 3 efficacy testing in humans
 - May allow efficacy based on animal data (at least two species)
- **Large/complicated clinical studies to demonstrate safety, immunogenicity, and efficacy**

Commercial Sector Concerns

- **Unusually hazardous risks, liability and indemnification issues**
- **Small volume of business and low annual production requirements**
- **Limited commercial opportunities for BD vaccines**
- **Stringent Bio-containment requirements**
- **Biological Warfare Convention inspection requirements**
- **Government contracting and regulatory oversight requirements**

Key Features of a National Vaccine Production Facility

- **Government control of production, availability, and distribution**
- **Meets high national security priority for additional BD vaccine production**
- **Establishes a second source for anthrax vaccine adsorbed (AVA) production**
- **Overcomes limited industry interest in BD vaccine production**
- **Gov't biosafety containment facilities provide supporting R&D**
- **Flexibility for emerging production technologies**
- **Operating contractor provides specialized expertise in vaccine production and regulatory requirements**

Challenges

- **Defining production capacity requirements**
- **Defining battlefield exposure levels for Biological Warfare (BW) agents**
- **Addressing emerging/changing requirements**
 - FDA regulations
 - DoD policy
- **Cooperative development with potential international and domestic partners**
 - Aligning requirements
 - Negotiating agreements
 - Avoiding schedule impacts

Assessing Risk

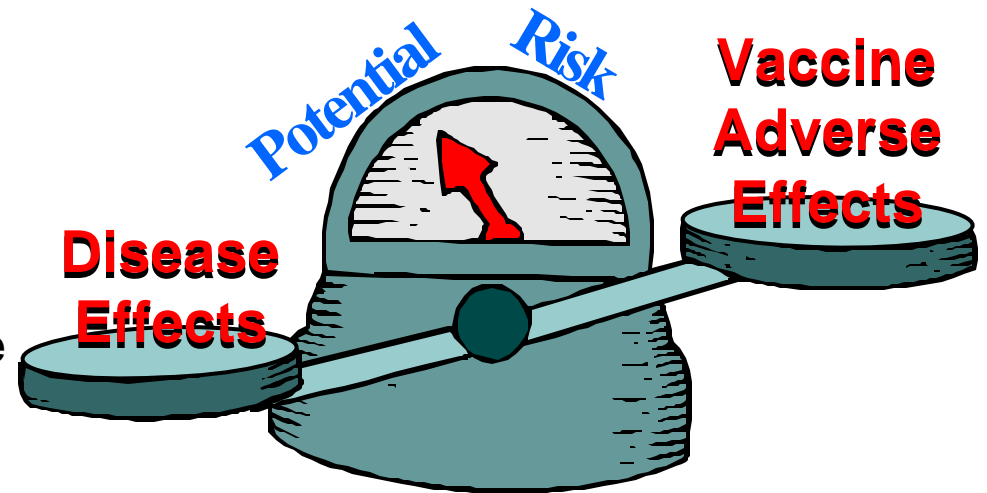
- Number of attacks against the U.S. military personnel with anthrax (or any biological weapon): **0**
- Probability (P) of attacks in the future against the U.S. military personnel with anthrax (or any biological weapon): **$0 \leq P \leq 1$**

Vaccine Use Risk Management Decisions

Naturally-Occurring Infectious Diseases

(Selected Prophylaxes)

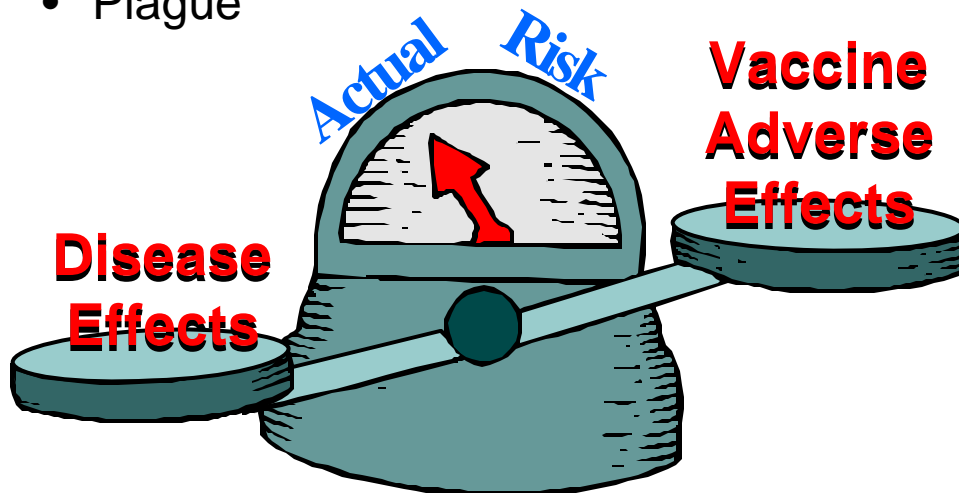
- Typhoid
- Yellow fever
- Malaria
- Diphtheria
- Tetanus
- Poliovirus
- Plague
- Hepatitis A virus
- Meningococcal disease
- Influenza vaccine
- Measles
- Mumps
- Rubella



Biological Defense Vaccines

- Anthrax Vaccine Adsorbed
- Botulinum Toxoids*
- Tularemia Vaccine*
- Smallpox vaccine (Vaccinia Virus, Cell Culture-derived)*
- Equine Encephalitis Virus Vaccines*

*Investigational New Drug (IND) status



A Complete and Comprehensive List of Risk-Free Military Operations and Activities

-
-
-
-
-
-
-
-

Limitations on Military Material Support for Civilians

- **Material designed to meet warfighter requirements may not be suitable for civilian use.**
 - Medical products must be fully licensed by the Food and Drug Administration and / or used with individual informed consent.
 - Military medical CB defense products assume a healthy adult population.
 - Some CB defense vaccines, pretreatments, and treatments may confound other medical treatments.
 - Classic “benefit-to-risk” decisions are not likely to support pre-exposure immunization of large populations against biological agents.
 - Voluntary compliance cannot be guaranteed for a large population.

Concerns for Using Biological Defense Vaccines

- **Vaccine use: Routine use vs. stockpile**
 - Limited shelf life for stockpile
 - FDA issues for maintaining license if site not involved in ongoing production
- **Undetermined health effects of administering multiple vaccines**
 - No adequate basis to assess safety, yet no basis for extraordinary concern
 - *Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces* (1996)
Institute of Medicine
- **Undetermined long-term health & safety effects**
- **Policy/Risk decision on vaccine types**
 - Live vaccines may be more effective, yet may have greater adverse effects (e.g., Oral vs. injectable polio vaccines)
- **No policy for immunizing civilian population**
 - Considerations include larger populations, pediatrics, geriatrics, immune-suppressed individuals

Parting Thoughts

- **Availability of vaccine based on several factors:**
 - Sustained resources to transition products from tech base and advanced development
 - FDA licensure of vaccine and production facility
 - Commercial interest likely to be limited – Biological Defense (BD) vaccines similar to orphan drugs
- **Implementation of vaccination**
 - Vaccination decisions will continue to have greater physiological consequences than non-medical (*e.g.*, mask on) decisions
 - Risk communication as important (if not more) than risk assessment